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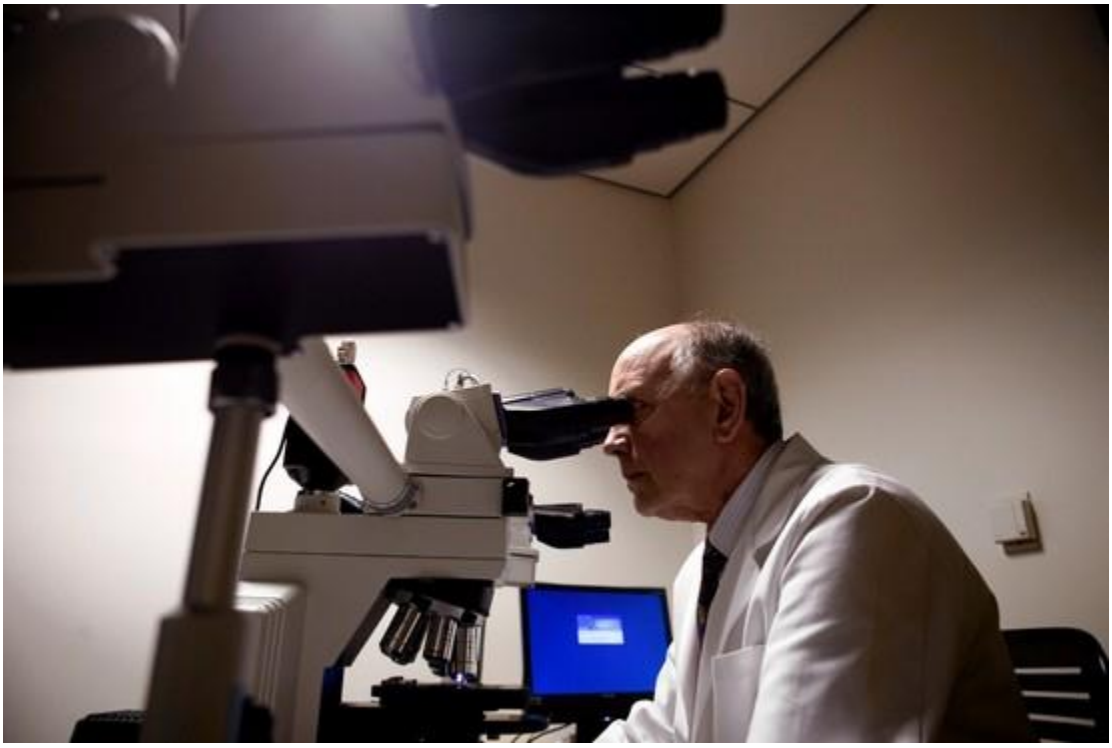
Lab Mistakes Hobble Cancer Studies But Scientists Slow to Take Remedies

By AMY DOCKSER MARCUS

Last year, cancer researcher Robert Mandic got news no scientist wants to hear.

After publishing a paper on a rare head-and-neck cancer, he learned the cells he had been studying were instead cervical cancer. He notified the journal Oral Oncology, which retracted the article.



Eros Hoagland for The Wall Street Journal

Pathologist David Tarin at the University of California, San Diego, where he studies breast cancer, Thursday.

"To base something on wrong data is bad, so it needs to be reported and I did," said Dr. Mandic, a researcher at the University Hospital Giessen and Marburg in Germany. "But it wasn't pleasant to call."

Dr. Mandic entered a largely secret fellowship of scientists whose work has been undermined by the contamination and misidentification of cancer cell lines used in research labs around the world.

Cancer experts seeking to solve the problem have found that a fifth to a third or more of cancer cell lines tested were mistakenly identified—with researchers unwittingly studying the wrong cancers, slowing progress toward new treatments and wasting precious time and money.

In hundreds of documented cases that undermine a broad swath of research, cancer samples that were supposed to be one type of tumor have turned out to be another, through either careless laboratory handling, mislabeling or other mistakes.

It is a problem hiding in plain sight. Warnings to properly test cancer cell lines have sounded since the 1960s, a decade after scientists started making human cancer cell lines.

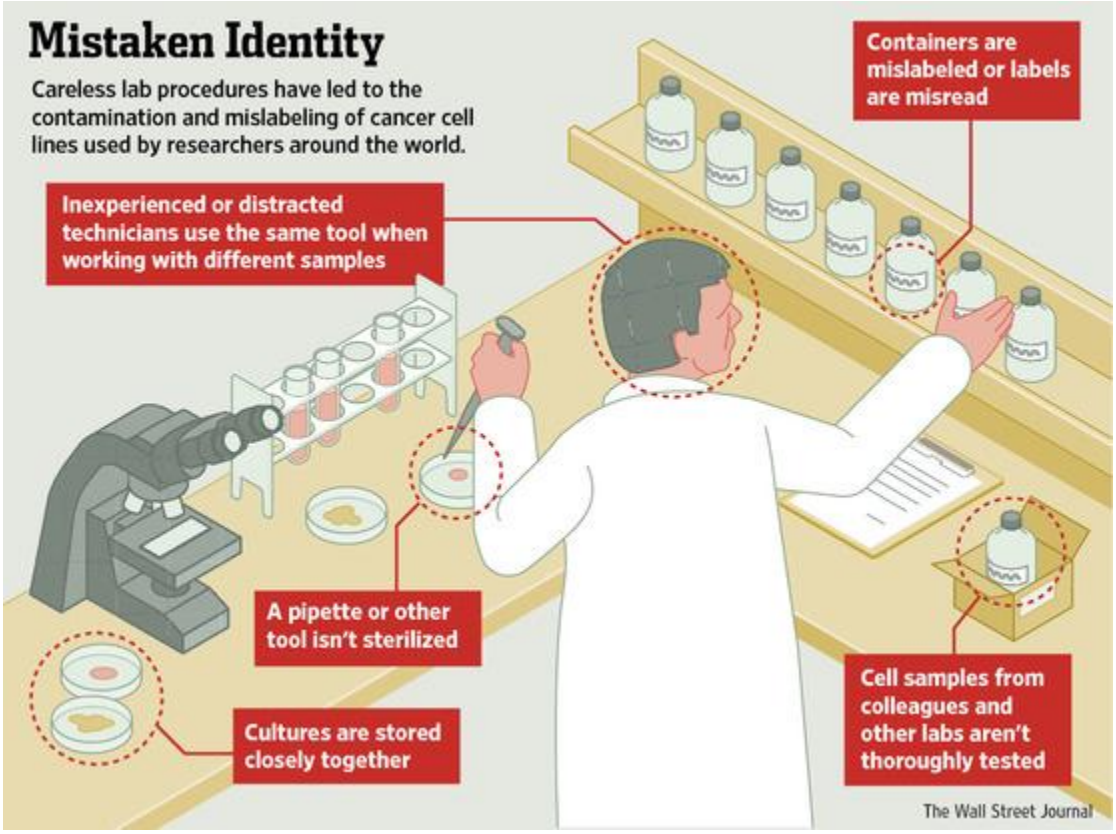
But researchers who yelled loudest were mostly ignored by colleagues fearful such a mistake in their own labs would discredit years of work.

Leaders in the field say one of the biggest obstacles to finding a cancer cure may not be the many defenses nature affords malignancies, but the reluctance of scientists to address the problem.

"Screaming and shouting, it doesn't do any good. No one takes any notice for reasons I don't understand," said John Masters, a professor of experimental pathology at University College London, UCL. "The whole ethos of science is to strive for the truth and produce a balanced argument about the evidence. Yet, all this crap is being produced."

Dr. Masters said cell banks report that 20% of cell lines sent for inclusion in their repositories for use by researchers are improperly identified. He was co-chair of an international committee of scientists that released voluntary guidelines this year to begin solving the problem. They call for, among other measures, routine profiling of cell lines using a DNA technique employed in forensics called "short tandem repeats," or STR.

Much of cancer research seeks answers to questions of basic biology, so the proper identification of cell lines may be less important, said Dr. Masters. But when seeking cancer treatment for a specific tumor, he said, such mistakes "are an utter waste of public money, charity money and time."



Worse, he added, "It may be causing drugs to be used which are inappropriate for that particular type of cancer."

Cancer research relies on cell lines that originate in patient tumors. The cells are usually grown in plastic containers and, with the proper nutrients, can live indefinitely in a laboratory. Scientists store them in freezers for years. The cells mimic particular kinds of tumors, giving researchers a way to understand what drives a disease or to test promising drug treatments.

It may take a year or more to find the right combination of nutrients to keep cancer cells growing. Once a line is established, scientists often share them with colleagues, who then grow them in their own labs. The problem is that many scientists don't test the cells when shipping or receiving a batch.

The most famous and ubiquitous human cancer cell line was the first—an aggressive, fast-growing cervical cancer taken from Henrietta Lacks of Maryland before her death in 1951. It has been shared with scientists world-wide in the decades since, playing a broad role in medical research spanning polio to hemophilia.

The so-called HeLa cells, named for Ms. Lacks, also have taken over other cancer cell lines, many times unknown to researchers.

These mix-ups are maddeningly difficult to pinpoint: an improperly sterilized pipette, a lab worker momentarily distracted, a misread label or a typo on a record sheet.

Cell repositories in the U.S., U.K., Germany and Japan have estimated that 18% to 36% of cancer cell lines are incorrectly identified. Researchers at Glasgow University and CellBank Australia found more than 360 such mistaken cell lines, including 100 that turned out to be the late Ms. Lack's cervical cancer cells.

"All of this sharing of cell lines, it's a bit like having unprotected sex," said David Tarin, a pathologist at the University of California, San Diego.

Dr. Tarin himself is at the center of a lingering debate over the true identity of a famous breast cancer cell line known as MDA-MB-435.

Dr. Tarin has spent 25 years working with that cell line—or so he thinks. A body of research suggests that MDA-MB-435 isn't breast cancer; many scientists now believe the cells growing in labs and used in decades of research are melanoma.

The line originated at the M.D. Anderson Cancer Center in Houston, using cells from a 31-year-old woman who died in 1976, less than a year after she was diagnosed. The cell line was among the most widely used in metastatic breast cancer research.

In 2000, scientists at Stanford University, working in collaboration with the National Cancer Institute, started testing the 60 cell lines in the institute's permanent collection.

Michael Eisen, then part of the Stanford team, said they found something surprising about the breast cancer cell line: genes that mimicked melanoma. "It stuck out as problematic," said Dr. Eisen.

At the time, the scientists didn't suspect contamination. They thought the breast cancer patient also might have had undiagnosed melanoma.

Other scientists, following up on the observations at Stanford, demonstrated that MDA-MB-435 behaved like melanoma because it likely was melanoma—in particular, a skin-cancer cell line called M14.

As word spread, Michael D. Johnson of Georgetown University Medical Center and a team of colleagues tested stocks of MDA-MB-435 from their lab and others around world. He said the group assumed their laboratory cell lines were the "real ones," and that other scientists' lines had been corrupted. Instead, the group found every one of the cell lines tested was melanoma, not breast cancer.

Decades of research had been built on insights from research using that cell line. Now, said Dr. Johnson, "I'm not going to use them to study breast cancer. I don't believe they are breast cancer."

Dr. Tarin disagrees, citing his own study that showed breast cancer tumors can have melanoma-like genes.

Increasingly, medical journals won't accept research on breast cancer involving the MDA-MB-435 cell line, throwing into question decades of experiments and innumerable published papers based on the line.

Seeking to solve the problem, a committee led by ATCC, a nonprofit group based in Manassas, Va., released guidelines this year to establish standards to authenticate cancer cell lines.

ATCC is working with the National Center for Biotechnology Information, a branch of the National Institutes of Health, to establish a central repository and database of cell lines that have undergone genetic testing and whose origins can be verified.

The National Institutes of Health have, so far, not required cell line authentication as a condition of receiving federal grants. The NIH in 2007 called for more stringent peer-review when cell lines are used in papers submitted for publication. Journals of the American Association For Cancer Research now require authors to disclose how and when their cell lines were tested.

One challenge is getting scientists to acknowledge their cell line is contaminated. The prevailing attitude, according to researchers, is that the other lab's cell line may be contaminated but not mine.

Osamu Tetsu, a head-and-neck cancer researcher at the University of California, San Francisco, did a study in 2009 that concluded all six known cell lines used by researchers studying adenoid cystic carcinoma were contaminated.

All of the work done on the rare cancer—published papers, research, drug studies—had been conducted with mislabeled cell lines, Dr. Tetsu concluded. He called the findings "catastrophic."

Jeffrey Kaufman, executive director of the Adenoid Cystic Carcinoma Research Foundation, said the group lost about $150,000 on a project that had to be scrapped. He alerted Dr. Mandic, who had a lab perform STR profiling on his cell line, which came from a colleague, who got it from another scientist a decade earlier. Tests revealed it was Ms. Lack's cervical-cancer cell line.

The scientist cited in Dr. Tetsu's paper as the source of one of the corrupted cell lines said his lab wasn't responsible. Ruy Jaeger of the University of São Paulo in Brazil wrote in an email to The Wall Street Journal that his cell line was, in fact, adenoid cystic carcinoma. He also pointed out he had not directly provided the line used in the published paper.

Dr. Tetsu said he tested a cell line created from Dr. Jaegar's line by a scientist in the U.S. The only way to resolve the dispute, said Dr. Tetsu, would be to perform STR profiling of Dr. Jaegar's cells and compare them to the DNA of the original cancer patient.

The problem is particularly damaging for research into such rare cancers as adenoid cystic carcinoma, which strikes 1,200 people in the U.S. each year. The lack of a good cell line slows research and few in the field have the time or resources to create new lines.

More broadly, the sharing of cell lines is such an intrinsic part of scientific culture, Dr. Tetsu said, that "it is almost impossible to stop."

University of Washington scientist Stanley Gartler warned about the practice in 1966. He had developed a pioneering technique using genetic markers that would distinguish one person's cell from another. Using the process, he tested 20 of the most widely used cancer cells lines of the era. He found 18 of the lines weren't unique: They were Ms. Lacks' cervical cancer.

"People were upset," said Dr. Gartler, who published his findings a year later in the journal Nature. "No one wants to admit they made a mistake."

Dr. Gartler, an 88-year-old professor emeritus, said a decade after publication of his findings he attended a conference and introduced himself to a scientist. Dr. Gartler recalled the man told him, "'I heard your talk on contamination. I didn't believe what you said then and I don't believe what you said now.' "

That became a long-held view. Nearly 40 years later, Dr. Masters, in a study of scientific papers published between 2000 and 2004, found nearly a 1,000 citations of the same contaminated cancer lines revealed in Dr. Gartler's 1966 findings, which have since been replicated many times using more advanced techniques. "They are either crooks or stupid," said Dr. Masters.

Financial donors to cancer research are unaware of the problem, Dr. Masters said, and "it would be a pity if money stopped going to cancer research" because scientists fail to test their cell lines, a procedure that costs about $200.

From San Diego, Dr. Tarin wrote to the ATCC to say his studies show that MDA-MB-435 is a breast cancer line, not melanoma. He has not heard back.

Yvonne Reid, who works for the ATCC and was a member of the committee that wrote the new guidelines, said, "It is hard to come down for one or the other" without testing tissue from the breast-cancer and melanoma patients who originated the cell lines.

Donald Morton, who was part of the team at the University of California, Los Angeles that in the 1980s grew the original melanoma line now believed to have contaminated MDA-MB-435, said his cell line has genetic markers that match the original patient with melanoma.

Dr. Morton, currently the melanoma program director at the John Wayne Cancer Institute in Santa Monica, Calif., said he would share frozen tissue samples from the melanoma patient with scientists seeking to test against contaminated cell lines.

His melanoma cells, Dr. Morton said, are indeed melanoma.

"What happened after that cell line left my lab," he added, "I cannot say."

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